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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,668	04/14/2006	Frank-Christophe Lintz	65177(45107)	1828

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EXAMINER	
HAGHIGHATIAN, MINA	
ART UNIT	PAPER NUMBER
1616	
MAIL DATE	DELIVERY MODE
08/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,668	LINTZ ET AL.	
	Examiner	Art Unit	
	MINA HAGHIGHATIAN	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-41 and 44-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-41, 44-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/16/08 has been entered.

Receipt is acknowledged of the Amendments and Remarks filed on 05/16/08. Claims 25 and 28 have been amended and claims 42-43 have been cancelled. No new claims have been added. Accordingly claims **25-41, 44-55** remain pending.

Claim Objections

Claim 27 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 25 recites a preparation that contains magnesium salt and/or a calcium salt, which are neutral isotonising agents. Thus the limitation of claim 27, “at least one substantially neutral isotonising agent” has already been presented in the parent claim 25.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 25-26, 29-30, 35-41 and 44-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malvolti et al (WO 03004005) in view of Hughes et al- The Lancet-2003 (Use of isotonic nebulised magnesium sulphate as an adjuvant to salbutamol in treatment of severe asthma in adults: randomized placebo-controlled trial) (Provided by Applicant in the IDS of 04/14/06).

Malvolti et al teach optimized formulations of tobramycin for aerosolization in the form of additive-free, **isotonic solution** whose pH has been optimized to ensure adequate shelf-life at room temperature. Said formulation can be advantageously used for treatment and prophylaxis of acute and chronic endobronchial infections (see

abstract). In a preferred embodiment a formulation is prepared containing 300 mg of tobramycin sulfate in 4 ml of half-saline aqueous solution (0.45% of sodium chloride) in order to have an osmolarity ranging from 280 to 350 mOsm/l and it has a pH between 4.0 and 5.5 (page 5, line 25 to page 6, line 3). Other formulations have been prepared using ¼ **normal saline** (see page 7). Malvolti et al disclose that the inventors of the patent EP 734249, it was discovered that "a further advantage of a **quarter normal saline**, i.e. saline containing 0.225% of sodium chloride with 60 mg/ml tobramycin is that this formulation is **more** efficiently nebulised by an ultrasonic nebuliser *compared* to tobramycin formulated in a solution of 0.9% normal saline (page 7, lines 11-15).

Malvolti et al also disclose a method of preparing the said formulations which includes the steps of adjusting the pH by adding an acid adjuvant such as sulfuric acid and also sterile filtering the solution (see pages 9-10). The prepared formulations are typically distributed in 2 ml polyethylene colorless unit dose vials under nitrogen purging (page 11, lines 11-12) and are administered by a nebulizer such as a jet PARI nebulizer (see page 14).

Tables 1 and 2 show a formulation that comprises between 67.5 and 82.5 mg/ml tobramycin.

Malvoti lacks disclosure on the addition of a magnesium or calcium salt.

Hughes et al disclose a trial that investigates the effect of isotonic magnesium administered as an adjunct to nebulized salbutamol. It is then concluded that "Our results showed that use of isotonic nebulised magnesium sulphate as an adjuvant to

salbutamol nebulizer solution results in an enhanced bronchodilator response in severs asthma. Administration of the salbutamol nebulizer solution with the magnesium adjuvant resulted in about twice the increase in FEV_1, than the same dose of salbutamol administered with an isotonic saline nebulizer solution (page 2116, col. 2, 1st and last paragraphs and page 2117, col. 1, 4th paragraph).

Malvolti et al does not anticipate the claims because it does not disclose a formulation that contains 2 mg/ml sodium chloride or less, and does not teach addition of a magnesium or calcium salts. However it does disclose using ¼ normal saline and it is disclosed that lower concentrations of sodium chloride in the said solution formulation are beneficial, thus one of ordinary skill in the art would have been able to optimize the concentration ranges of tobramycin and sodium chloride to prepare a more effective formulation. Furthermore, Hughes et al disclose that addition of magnesium sulphate is highly advantageous in treating asthma with salbutamol and that it enhances bronchodilator effect of salbutamol. Thus one of ordinary skill in the art would have been motivated to have combined the formulations of Malvolti et al and magnesium sulphate of Hughes et al with a reasonable expectation of successfully preparing an effective formulation for respiratory disorders. In other words, **all the claimed elements** were known in the prior art and one skilled in the art could have **combined the elements** as claimed by known methods with no change in their respective functions, and **the combination would have yielded predictable results** to one of ordinary skill in the art at the time of the invention.

Furthermore, Malvolti lacks certain specifics of the claimed nebulizer or packaging such as closure elements and nose pieces, however it is considered while the said limitations are not expressly disclosed, they exist in the jet or ultrasonic nebulizers and packages disclosed by the prior art. It is also noted that the instant claims are drawn to "a sterile liquid preparation" and the packaging or mode of administration are not patentable elements of a formulation.

Claims 25-26, 29-30, 36-41 and 44-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Montgomery (6,083,922) in view of Hughes et al- The Lancet-2003 (Use of isotonic nebulised magnesium sulphate as an adjuvant to salbutamol in treatment of severe asthma in adults: randomized placebo-controlled trial) (Provided by Applicant in the IDS of 04/14/06).

Montgomery teach a method of treating chronic tuberculosis using a preservative-free concentrated tobramycin aerosol formulation delivering tobramycin to the lung endobronchial space (see abstract). The formulations for use in the said methods comprise from 40 to 800 mg of tobramycin in 5 ml of quarter normal saline. This corresponds to 8-160 mg/ml (col. 10, lines 9-17). The tobramycin formulations comprising 60 mg/ml of ¼ **NS** have an osmolarity in the range of 165-190 mOsm/l (col. 10, lines 52-55). The pH is between 5.5 and 7.0 (col. 10, lines 60-67).

Montgomery discloses that the formulations are administered by nebulizers such as jet and ultrasonic nebulizers. A jet nebulizer works by air pressure and an ultrasonic

nebulizer works by piezoelectric crystal. Examples of the said nebulizers include Pari LC and Pari LC plus (see col. 12, lines 1-59). Examples 1-3 disclose the ingredients and amounts of the formulations. Other than tobramycin and saline, sulfuric acid is present. Montgomery also states that "Higher amounts of tobramycin was delivered when tobramycin was formulated in ¼ **diluted saline** than tobramycin formulated in *full strength nondiluted saline"* (see col. 16, lines 17-19). The formulation is stored in polyethylene LDPE vials in foil overpouch (col. 16, lines 60-65).

Montgomery does not teach addition of a magnesium or calcium salt.

Hughes et al disclose a trial that investigates the effect of isotonic magnesium administered as an adjunct to nebulized salbutamol. It is then concluded that "Our results showed that use of **isotonic nebulised magnesium sulphate** as an adjuvant to salbutamol nebulizer solution results in an enhanced bronchodilator response in severs asthma. Administration of the salbutamol nebulizer solution with the magnesium adjuvant resulted in about twice the increase in FEV_1, than the same dose of salbutamol administered with an isotonic saline nebulizer solution (page 2116, col. 2, 1st and last paragraphs and page 2117, col. 1, 4th paragraph).

Montgomery does not anticipate the claims because it does not disclose a formulation that contains 2 mg/ml sodium chloride or less, or the addition of a magnesium or calcium salt. However it does disclose using ¼ normal saline and that ¼ **normal saline is advantageous** because it allows for higher amounts of tobramycin

being delivered, thus it would have been clear to one of ordinary skill in the art that lower concentrations of sodium chloride in the said solution formulation would be beneficial. One of ordinary skill would have been able to optimize the concentration ranges of tobramycin and sodium chloride to prepare a more effective formulation for aerosol administration. Furthermore, Hughes et al disclose that addition of magnesium sulphate is highly advantageous in treating asthma with salbutamol and that it enhances bronchodilator effect of salbutamol. Thus one of ordinary skill in the art would have been motivated to have combined the formulations of Malvolti et al and magnesium sulphate of Hughes et al with a reasonable expectation of successfully preparing an effective formulation for respiratory disorders. In other words, **all the claimed elements** were known in the prior art and one skilled in the art could have **combined the elements** as claimed by known methods with no change in their respective functions, and **the combination would have yielded predictable results** to one of ordinary skill in the art at the time of the invention.

Claims 27-28 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malvolti et al (WO 03004005) in view of Hughes et al as applied to claims 25-26, 29-30, 35-41, 44-55 above, and further in view of Wiedmann et al (5,747,001).

Malvolti et al and Hughes et al, discussed above lack specific disclosure on adding other isotonising agents and surface active adjuvants.

Wiedmann et al teaches an aerosol comprising droplets of an aqueous dispersion of nanoparticles, comprising an active agent having a surface modifier on the surface thereof (see abstract). The said modifiers include calcium stearate, magnesium aluminum silicate, lecithin (phosphatides), n-dodecyl ß-D-maltoside and tyloxapol (see cols. 3-4). The said aerosols are typically administered by nebulizers such as jet and ultrasonic nebulizers (see col. 3, lines 17-28).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the formulations of the combined references by adding the surface modifiers/adjuvants as taught by Wiedmann et al with a reasonable expectations of successfully preparing formulations for inhalation that are stable and easy to flow. In other words, this rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients, In re Sussman, 1943 C.D. 518.

Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Malvolti et al (WO 03004005) as applied to claims 25-26, 29-30, 35-41, 44-55 above, and further in view of Azria et al (5,759,565).

Malvalti et al and Hughes et al, discussed above, lack specific disclosure on viscosity of the formulations.

Azria et al teach pharmaceutical compositions for nasal administration, comprising an active and a surfactant in a liquid carrier. The said compositions should possess appropriate isotonicity and viscosity. The preferred osmotic pressure is from about 260 to about 380 mOsm and the viscosity is from about 2 to about $4x10^{-3}$ Pa.S (see col. 4, lines 5-30).

It would have been obvious to one of ordinary skill in the art at the time the invention was made given the general formulations of the combined references on nebulizer solution formulations comprising an active agent and surfactants to have looked in the art for suitable and appropriate isotonicity and viscosity for the formulations as taught by Azria to prepare and effectively deliver a solution formulation to the mucosa for maximum absorption and systemic distribution.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments with respect to claims 25-55 have been considered but are moot in view of the new ground(s) of rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINA HAGHIGHATIAN whose telephone number is (571)272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mina Haghighatian/

Mina Haghighatian
Primary Examiner
Art Unit 1616